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Abstract

Objectives: Treatment for childhood Complex Regional Pain Syndrome (CRPS) is associated with long-term recovery. The present study aimed to investigate the long-term biopsychosocial status and quality of life in young adolescents and adults after the treatment of childhood CRPS.

Methods: A 4 year follow-up of individuals with childhood-CRPS, type 1 (n=22; age:12 years (years) [median] at treatment and 17 years at follow-up) was completed. Biopsychosocial status and quality of life were assessed with structured interviews, using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the Strengths and Difficulties Questionnaire (SDQ), the Pediatric Pain Coping Inventory (PPCI), and the Pediatric Quality of Life Inventory (PedsQL). Comparisons were made with normative samples of age-matched controls.

Results: CRPS at follow-up was still present in seven out of 22, and non-CRPS pain symptoms were found in 12 out of 22 individuals. Signs of mental health pain-related problems, including phobias and obsessive-compulsive disorder, were observed in ten out of 19 individuals. Mental well-being, social functioning, and quality of life (SDQ and PedsQL) were independent of pain status ($p>0.05$). Adaptive pain coping strategies were utilized regardless of pain status (PPCI). Social functioning ($p<0.01$) and the quality of life ($p=0.01$) were attenuated and statistically significantly poorer than healthy age-matched young adults but better than for fibromyalgia subjects.

Conclusions: A subset of individuals treated for childhood-CRPS, type 1 experiences long-term consequences of persistent pain, a decrease in quality of life indicators, and demonstrates significant psychosocial issues. Childhood-CRPS is suggested to be associated with long-term psychosocial consequences and poorer quality of life than found in age-related healthy peers. Subjects treated for childhood CRPS may need a longer clinical follow-up attempting to preclude relapse of CRPS and non-CRPS pain.

Keywords: adolescent; child; chronic pain; complex regional pain syndromes; mental health; quality of life.

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Introduction

Complex Regional Pain Syndrome (CRPS) is a debilitating chronic pain condition in children and adults with a prevalence of 5.4–26.2 per 100,000 person-years [1]. For the pediatric population, CRPS often significantly impacts the child's life requiring a specialized and multifaceted

treatment [2, 3]. Intensive physical therapy combined with psychotherapy/cognitive behavioural therapy is often employed and seen as the primary pathway to a seemingly full recovery [4, 5]. CRPS is characterized by regional and seldom dermatome-related, spontaneous or evoked, and often severe pain [3]. There are two types of CRPS either without (Type 1) or with (Type 2) a definable nerve lesion [3]. The aetiology and pathogenesis of CRPS are unknown though several factors seem to be important in triggering and maintaining symptoms, such as genetics determinants, inflammatory and immune response, and psychological factors [6]. There might be differences between children and adult CRPS, where psychological factors may play an essential role in the pathogenesis of this seemingly 'physical' condition for children [2, 7]. It is not yet determined whether the evoked pain response in CRPS leads to emotional impairment and psychosocial dysfunction, or rather that preexisting emotional impairment and inexpedient psychosocial coping mechanisms contribute to the development or the maintenance of the symptoms [2, 8].

The affective expression of reported high pain intensities often is incongruent with the absent biological findings [2, 3]. Moreover, the ongoing beliefs regarding clinical differences between the adult and pediatric populations for pediatric CRPS may not be as true as earlier perceived [9]. Differences have been suggested, namely that the pediatric population has a higher incidence of lower extremity involvement, it is less likely that the onset of symptoms is preceded by trauma, and the female gender is disproportionately overrepresented [10–13]. Moreover, pediatric CRPS-treatment is commonly perceived to have a far better outcome than adults with a success rate of up to 97% in the short term with a mean follow-up of 15.4 weeks [3, 14]. This has been contradicted by an electronic survey that indicated that the prognosis of childhood-onset CRPS is less favourable in the long-term with a relapse rate similar to adults of 33% and decreased quality of life to follow [9]. Pediatric patients with CRPS have also been believed to have preexisting emotional impairments and psychosocial dysfunctions [3], but some studies suggest that these children have similar psychological functioning and that levels of depression and anxiety are similar to children with other pain conditions [2, 10]. This suggests that psychological aspects are not causal to the development of CRPS but rather a consequence of CRPS. It is suggested that other occurrences such as prior family-related life traumatic events might be causal [2, 10, 15] but the long-term biopsychosocial status in children treated for CRPS remains widely unexplored.

In this exploratory study, we examined the long-term pain status of initially cured CRPS-patients. We compared the biopsychosocial status and quality of life according to pain status and to normative data when possible.

Methods

Subjects

This study was a retrospective cohort study, where former pediatric CRPS-patients were included as subjects recruited as a convenience sample from two University hospitals from the Capital Region of Denmark. Children were aged 7–18 years were included if they were diagnosed with CRPS 1, according to the Budapest Criteria [16], between 2007 and 2017. The initial CRPS treatments were carried out by multidisciplinary teams of anesthesiologists, pediatric orthopaedic surgeons, psychologists, and physiotherapists in close collaboration with hospital school teachers, social workers, and nurses. Patients from both hospitals were treated with intensive physiotherapy in two sessions lasting 2 h daily. This was performed in the morning and evening. Selected patients had a peripheral nerve block for continuous pain relief during treatment before starting their rehabilitation process. Patients were trained by psychologists in strategies of pain coping and in modifying negative cognitive emotions, distortions, and behaviours in addition to their physiotherapy treatment. The average duration of in-hospital treatment was three weeks (range:1–11 weeks). Patients continued their physiotherapy during and after in-hospital treatment. They also attended school classes at the hospital.

Exclusion criteria for participating in the present study were ongoing pregnancy or participating in other studies affecting their current pain status. We contacted potential subjects through their parents for inclusion after a formal invitation by letter, and following acceptance, their medical records were screened according to the inclusion and exclusion criteria. If eligible, the former patients were included as subjects.

Questionnaires

The subjects were invited for a clinical evaluation and a structured interview, including questionnaires. The latter was targeted towards the CRPS, pain status and biopsychosocial status using a tailored pain and mental health questionnaire, the Strengths and Difficulties Questionnaire (SDQ), the Pediatric Pain Coping Inventory (PPCI), and the Pediatric Quality of Life (PedsQL). Depending on the child's age, parents were asked to assist in filling in the questionnaires, specifically since some of the questions regarded their previous CRPS– condition and former treatment, which might be difficult for the subjects to remember. The tailored pain questionnaire was adapted – but unvalidated for our native language – from a questionnaire used at the local hospitals. This was slightly altered to focus on current pain to determine whether the current pain was related to CRPS or related to other pain conditions. The subjects were separated into three groups related to the CRPS and pain status:

- **CRPS+:** Subjects with symptoms of CRPS at the time of testing and expressing that CRPS was still influencing their daily life.
- **CRPS–:** Subjects without symptoms of CRPS at the time of testing and expressing that CRPS was no longer affecting their daily life.
- **CRPS|OP:** Subjects without CRPS symptoms at the time of testing but experiencing other non-CPRS-related pain (OP) conditions that affected daily life.

We also included structured clinical questions focusing on mental health, daily life, and social coping. These questions were selected items by specialized clinicians treating CRPS from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) used in our clinical practice for clinical evaluation of anxiety, depression, phobia, self-damage, and traumatizing events [17]. There were seven specific questions

concerning pain-related anxiety, ten related to depression symptoms in the last 14 days, one related to specific anxiety and related social phobia, six related to generalized anxiety, fifteen related to panic disorders, four related to obsessional behaviour, one related to previous assault, seven related to post-traumatic stress syndrome, one related to self-harming behaviour, four related to suicidal thoughts and one related to other current medical treatment and psychotherapy. In general, if the subjects gave an affirmative answer to more than half of the questions, then we considered them as having symptoms of this mental disorder [18]. For depression, if the subject within the last 14 days could answer yes to one of two questions, then a minimum of five out of ten symptoms would also need to be present for the subject to fulfill this criterion. For specific anxiety, we inquired about phobias of social anxiety, claustrophobia, heights, needles, clowns, sailing, but questions were not limited to these specific areas. For general anxiety disorder, if the subject answered yes to two questions, and had at least one out of six symptoms present within the last 6 months, then the subject would fulfil this. For panic disorder, the subject had to have experienced at least four out of 12 symptoms in a limited period with acute development and peak within ten min. For Obsessive-Compulsive Disorder (OCD), if the subject had at least three out of four symptoms present, then the subject would fulfill this criterion.

SDQ is a brief, standardized emotional and behavioural screening questionnaire for testing children and adolescents to evaluate mental well-being and functioning in daily living [19]. The five dimensions are social strengths, emotional symptoms, behavioural symptoms, hyperactivity/attention difficulty, and difficulty with peers. These were evaluated by 25 items with three graded choices, and four additional questions with four graded choices. The subject was rated from choices of how well the statements suited their personality, and a score was calculated from these. The SDQ is designed to capture the perspective of the subject involved, the caretakers, and school relations perceived by teachers. However, we chose not to evaluate the perceived status by teachers since the teacher might not remember the child retrospectively or would be unattainable.

PPCI addresses how the child or adolescent responds to and copes with pain [20]. This questionnaire investigates the dimensions of cognitive self-instruction, problem-solving, distraction, social-seeking behaviour, and catastrophizing/helplessness. PPCI consists of four initial open initial questions, where the subject can give more elaborate and free answers to what they think, do, ask for, and wish for when they experience pain. Forty-one additional questions address the above-mentioned areas of pain coping strategies, where answers are rated from 0 to 2. A high score indicates greater use of coping/adaptive strategies. There are two age-appropriate versions of a child self-report and a parent proxy report.

PedsQL (Generic Core Scale 4.0) assesses health-related quality of life in healthy children and adolescents with acute and chronic health conditions. This questionnaire investigates the dimensions of the physical, emotional, social, and school/work functioning of the subject. These were evaluated by 23 items with five multiple choices with a score calculated by transforming answer choices (0–4) into a numerical scale from 0 to 100. This numerical score indicates a health-related quality of life (HRQOL). The PedsQL is developed in six age-appropriate versions with a child self-report and a parent proxy report [21]. We translated the questionnaire into Danish for this study using a formal procedure of forward and backward translations, comparison of original and backward translation, cognitive interviews, and discussion [22].

Comparisons to normative materials for psychosocial status and quality of life

Comparisons using Welch's t-test was used to between normative data from healthy young adults for mental disorders by the DSM-IV [23], mental well-being and functioning in daily living by the SDQ [24, 25] and health-related quality of life by the PedsQL [26]. Normative data from young adults with fibromyalgia were also used for comparison for the health-related quality of life.

Statistical analyses

For statistical analyses, the Chi-square test was conducted for differences in the distribution of gender and location of CRPS as well as the number of relapses and pain status. The Mann-Whitney U test was performed for comparing the pain status of CRPS+, CRPS– and CRPS|OP. The Mann-Whitney U test was performed for comparison across the dimensions and total scores for the groups of CRPS+, CRPS– and CRPS|OP for both children and parental evaluations as well as between the dimensions from children and parental evaluations. The Welch's t-test was conducted when our results were used to compare the CRPS subjects to the normative data from previous studies. We considered a p-value of <0.05 as indicating a statistically significant difference. Values are median (IQR) unless otherwise indicated. An *a priori* sample size estimate was not made due to the exploratory nature of our study. Data imputing was not performed. Statistical evaluations were performed using IBM SPSS Statistics, Version 22 (IBM, Richmond, VA, USA).

Ethics

The regional committee on health research ethics approved the study (No. H-17026983). We obtained oral and written consent according to national guidelines and following the Helsinki II declaration for biomedical research involving humans. No commercial or public financial support was received during the study.

Results

Thirty-eight patients were treated from 2007 to 2017 and were included in the study as potential subjects. We excluded three patients since their contact information was unavailable. Thirty-five patients and their parents were then contacted by phone. Twelve patients declined to be included since they were unable to allocate time for participating. We screened the remaining medical journals for eligibility, and one patient was excluded due to an erroneous diagnosis of CRPS. There were no significant differences in the age ($p=0.22$) and gender ($p=0.74$) distribution between the included and excluded former patients. Twenty-two of the 38 potential subjects were enrolled as subjects for evaluation by interviews and questionnaires. Figure 1 shows a flow chart of the enrollment process.

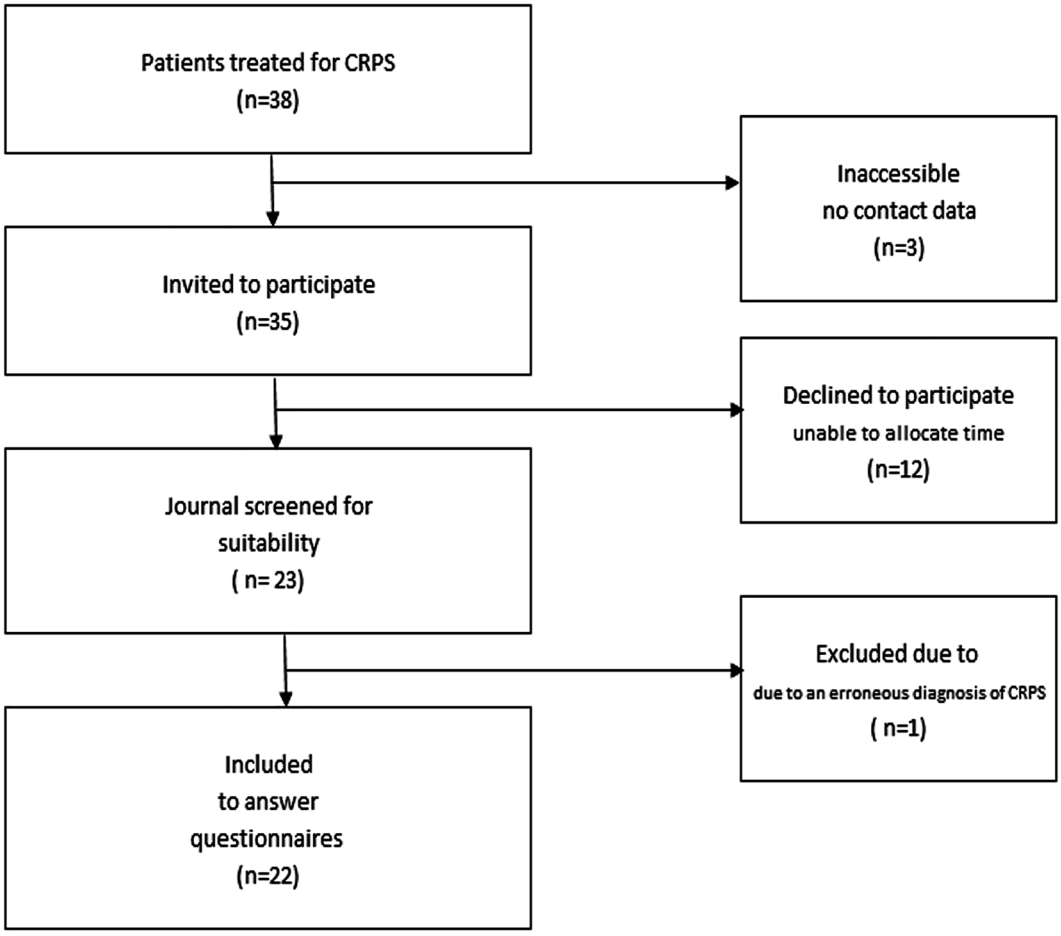

Figure 1: Flowchart of the inclusion process.

The subjects had a median (IQR) age of 12 (11–15) years at the time of treatment and the median age at the time of assessment was 17 (14.75–19) years. The median time between treatment and evaluation was 4 (2–5.25) years. The gender ratio (F/M) was skewed 6.3 (19/3) towards more females than males. Table 1 shows the CRPS site, current CRPS-status, and medication indications.

Table 1: Initial anatomical CRPS site, additional treatment for CRPS after initial treatment if any, current CRPS and pain status, and current medical treatment if any.

Injury site		Current status		Treatment using medication	
Foot	14	CRPS now		Strong pain	2
Lower extremity	6			Nerve pain	1
Hand	1	Yes	7	Agitation	2
Hand and foot	1	No	15	Depression	0
				Anxiety	1
Secondary CRPS		Other pain		ADHD	1
treatment				No medication	17
Yes	11	Yes	13		
No	11	No	9		

Questionnaires

The degree of completion of the questionnaires for the subjects (aided by the parents) and the parents only is illustrated in Table 2. Since the PPCI is constructed and validated for children only, subjects older than 18 were not requested to complete this questionnaire, hence the lower overall completeness of twelve subjects.

Pain status

The subjects were distributed in the three groups according to current pain status and the state of CRPS with seven in

Table 2: The number of completed questionnaires by the subjects (with parental assistance) and by parents only (parent-proxy).

	Subjects	Parents
Pain questionnaire	21	–
PedsQL	21	13
PPCI	12	12
SDQ	19	12

CRPS+, seven in CRPS– and eight in CRPS|OP. Medical records were evaluated to confirm that the anatomical sites of the current CRPS were similar to the prior CRPS locations.

All CRPS+ received secondary treatment for a recurrence of CRPS symptoms at a later stage. For both CRPS+ and CRPS|OP pain, eleven subjects had received secondary treatment due to the recurrence of pain symptoms. In the CRPS+-cohort, five out of seven also experienced other pain than CRPS symptoms, such as back and knee pain, thus adding up a total of twelve subjects having other pain (CRPS+ with other pain and CRPS|OP). The CRPS–|OP-cohort experienced (other) pain originating from a congenital spinal disorder, severe back pain, foot pain related to sports activity or foot deformity, and calf pain from an insertion enthesopathy of the distal part of the triceps surface muscle. In addition, one subject had an ongoing investigation of multiple sclerosis. In the CRPS– group, six out of seven were symptom-free after the first (initial) CRPS treatment.

Table 3: The ratio of subjects with specific mental health issues when evaluated by the DSM-IV of the mental health status according to the DSM-IV questions between CRPS+ and CRPS|OP vs. CRPS- and the p-values when comparing the combined group of CRPS+ and CRPS|OP with CRPS–.

	Ratio
Depression	3/19 (0.16)
Phobia	8/19 (0.42)
General anxiety	3/19 (0.16)
Panic disorder	6/19 (0.32)
OCD	6/19 (0.32)
Sex assault	2/19 (0.11)
PTSD	1/19 (0.05)
Self-harm	6/19 (0.32)
Suicidal thoughts	5/19 (0.26)
Total DMS IV	10/19 (0.53)
Other treatments	8/19 (0.42)

Mental health (DSM-IV)

Nineteen subjects completed the structured clinical interviews with selected questions from the DSM-IV. Ten out of nineteen subjects demonstrated one or more symptoms of affected mental health, according to our interviews based on DSM-IV. Almost half had symptoms of phobias (8/19), and one-third had symptoms of panic disorder (6/19), one-fourth have had suicidal thoughts (5/19), and self-harming behaviour (5/19), and one-sixth experienced general anxiety (3/19). However, these were not statistically significant when evaluated across the groups. The ratio of affected mental health status between CRPS+ and CRPS|OP vs. CRPS– groups are shown in Table 3. Figure 2 presents the mental health status in the number of subjects according to their pain status when divided into the three groups. The comparisons between the pooled cohorts with pain (CRPS+ and CRPS–|OP) vs. the cohort without pain (CRPS–) were not statistically significant.

Strengths and difficulties questionnaire (SDQ)

The five dimensions of the SDQ for the 19 subjects when divided into CRPS+, CRPS–, and CRPS|OP are illustrated in Figure 3. We demonstrated no significant overall difference between groups in total scores for CRPS+, CRPS–, CRPS|OP

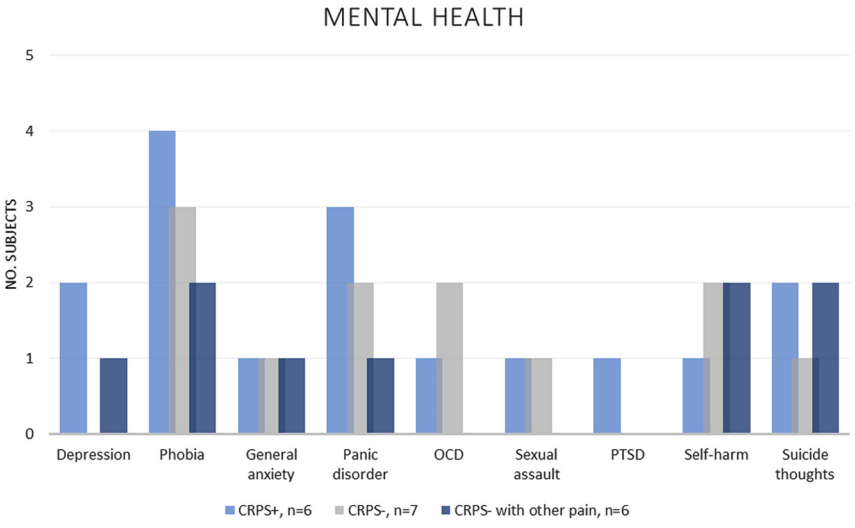

Figure 2: Mental health status in the number of subjects with the conditions when divided into CRPS+ (light blue) and CRPS– with (grey) or without other pain (dark blue). Not all sub-categories of the mental health status were represented in the three groups related to the CRPS and pain status, thus indicated by non-representation in the sub-categories in the figure.

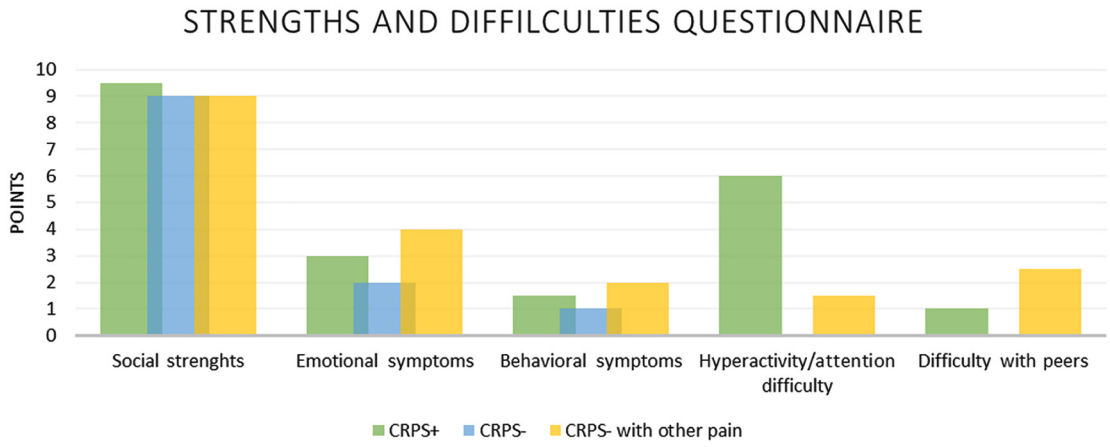

Figure 3: The dimensions of the SDQ for the CRPS+, CRPS–, and CRPS|OP groups, where the maximum score for each dimension was 10 points. A high score indicates greater use of adaptive coping strategies.

when evaluated by the child and the parents (Mann-Whitney U test). For the specific dimensions, there were no significant differences for 'social strength', 'emotional symptoms', 'behavioural symptoms', 'hyperactivity', and 'difficulty with peers' when evaluated by both child and parent. However, the 'social strength' was significantly lower for CRPS+ ($p=0.02$), for CRPS|OP ($p=0.03$), and CRPS– ($p=0.03$) when compared to the other dimensions and when evaluated by the child. When evaluated by the parent, the 'social strength' also was significantly lower for CRPS+ ($p=0.04$) and CRPS– ($p<0.01$) when compared to the other items, but not for CRPS|OP ($p=0.18$).

The median total effect score for well-being and social function was 1 (0–3) for the CRPS+, 0 (0–1) for the CRPS|OP, and 0 (0–2) for the CRPS–. The subjects with affected well-being and social function indicated that these negative influences had lasted at least 1 year.

Pediatric pain coping inventory

Twelve subjects and 12 parents filled in the PPCI. Figure 4 presents the number of subjects fulfilling the items of the PPCI when divided into CRPS+, CRPS– and CRPS|OP. When tested with the Mann-Whitney U test, there was no significant difference between groups in total scores for CRPS+, CRPS–, CRPS|OP. There were no other significant differences in the specific dimensions between the three groups,

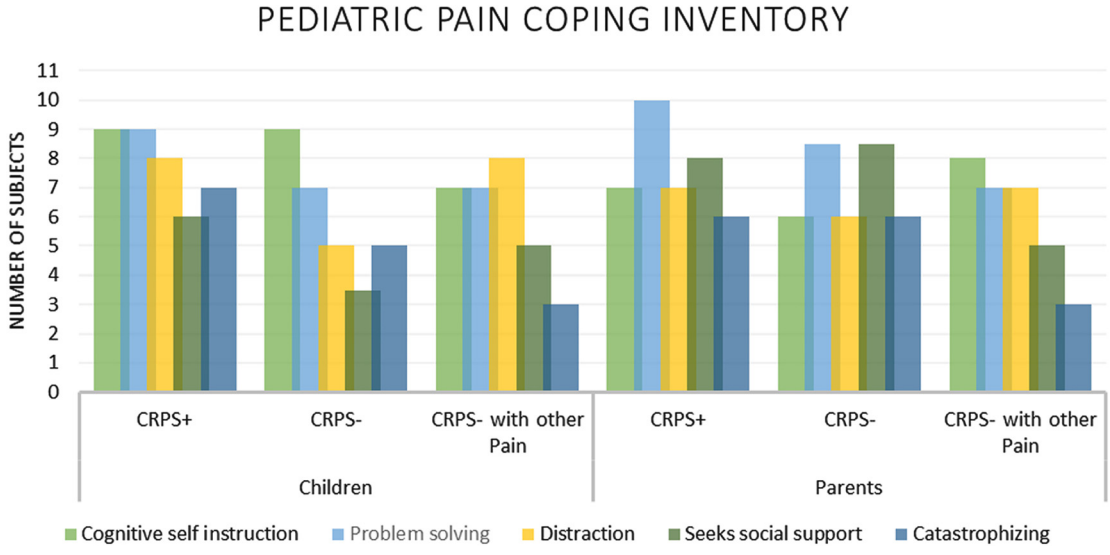

Figure 4: (A) The number of subjects fulfilling the items of the PPCI when divided into CRPS+, CRPS-, and CRPS|OP, when evaluated by the subjects (left) and the parents (right).

except for 'distraction' when evaluated by the parents for the CRPS+ group, which was lower compared to the CRPS– group (p=0.03). Children and parents had no significant differences using the Mann-Whitney U test in the total score as well as an overall evaluation of the four items of PPCI for CRPS+ and CRPS.

Pediatric quality of life

Twenty-one children and 13 parents completed the PEDSQL. There were no significant differences between the three groups. There was a significant difference in school functioning between children and parents, where the parental evaluation was lower than for the children (p<0.05). Otherwise, there was no statistical significance when comparing total scores as well as the other three subitems between children and parents.

Comparison to normative data

We compared our results to normative data of previous studies using Welch's t-test [23–26]. When compared to the general population of healthy young adults aged 12–18 years (n=1,253,846) and evaluated by the *DSM-IV*, the general prevalence of psychological disorders is 0.3%, and of depression and anxiety 0.6%, as opposed to half of our population [23]. When comparing the mental well-being and functioning by *SDQ*, the dimensions were apparently within the normal range or close to age-related healthy young (n=5,898), but when examined statistically, there was a significant difference for social strength (p<0.01), hyperactivity (p=0.01), and the total score (p<0.01) [25]. When comparing normative data on *quality of life* with data from our study, the quality of life for subjects was lower than for healthy young adults (n=1758) but better than when diagnosed with fibromyalgia (n=57) [26]. Figure 5 presents a comparison between the subjects with CRPS and a group of young adults with fibromyalgia and healthy young adults, respectively [26]. When compared to an age-matched group of healthy young adults and a group with fibromyalgia, and when evaluated by the subjects themselves, the scores were 13 points lower. When compared to an age-matched group of healthy young adults and a group with fibromyalgia and when evaluated by the parent, the scores were similar and 27 points lower, respectively. In fibromyalgia, there were significant differences when evaluating the total score (p=0.01), emotional (p=0.03), and social score (p=0.02) by the child, as well as for *all* dimensions when evaluated by the parent [26]. In typically developed children, there were significant differences when evaluating the total score (p=0.01), physical function (p=0.0006), and school function (p=0.03) by the child but no significant differences for all dimensions were found when evaluated by the parents.

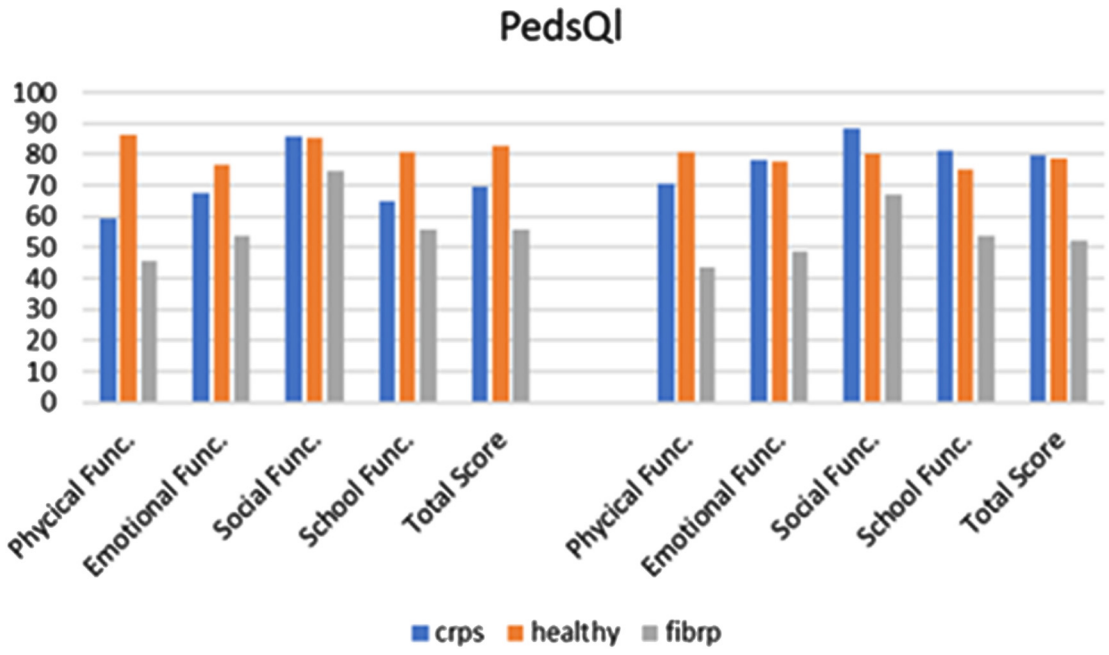

Figure 5: Comparison of scores of the PedsQL for the subjects (n=22) and a cohort of healthy young adults (n=1758) and young adults with fibromyalgia (n=57) for children (left) and adults (right).

Discussion

This exploratory study found that seven out of 22 well-treated CRPS children had the same CRPS symptoms at a 4 year follow-up and that more than 12 out of 22 children had other pain affecting their daily life. In this study, we were unable to report statistically significant differences in long-term bio-emotional and psychosocial status and quality of life when evaluating them according to their pain status even without applying statistical measures to reduce Type I error as Bonferroni corrections. However, this might be due to the low number of subjects and sub-categorizing into three groups depending on pain status, thus making the results of the statistical analyses difficult to interpret, and obtaining statistical significance would still be fraught with uncertainty due to type I error. However, we prioritized describing this component of other pain due to the clinical impact in this cohort of young adults treated for childhood CRPS. As a consequence, our study is hypothesis-generating and should be interpreted as such.

Reoccurrence of CRPS after successful childhood treatment

The results from the current study indicated a somewhat poorer outcome after pediatric CRPS when compared to the literature. Our relapse rate of childhood CRPS in the current study is higher than described by Sherry et al. [5], who had a success rate of 88% after at least 2 years. The current results resemble Stanton-Hicks [14] with no significant differences in the number of treated relapses or pain status when compared to the study by Tan et al. [11]. Tan et al. [9] also found attributed (pain) symptoms in 63% of the population, which is similar to the current study of 60% with other pain symptoms, whereas Sherry et al. [5] reported other pain in 4%. The perceived good outcome is probably ascribed to the initial good response rate of 97% [14], but longer follow-up rates of up to 4 years are necessary to ensure adequate monitoring for relapse of CRPS. In our study, we had a follow-up of up to 5.25 years with a median follow-up of 4 years. We had a follow-up from 2 years, whereas 16/22 had a follow-up of more than 3 years, which reflects the point that a longer follow-up is needed. Additionally, it is of paramount importance to be able to treat other pain states affecting daily living, which were seen in over half of the seemingly healthy young adults. In our population, 42% of the subjects had ongoing pain-related medical or psychological treatment, reflecting the need for both long-term monitoring and treatment. However, one-third had complete remission after one cycle of treatment for CRPS. However, direct comparison in outcomes is biased, since there are differences regarding treatments as i.e. treatment duration and treatment intensity as a general when comparing outcomes as pointed out by Bialocerkowski et al. [27].

Comparison to previous data on CRPS, normative data and limitations

In our population, we found that subjects with former childhood CRPS had a high relapse rate of CRPS and had other pain. They used adaptive pain coping strategies. For pain coping mechanisms evaluated by the PPCI, all subjects, regardless of subcategorization, utilized adaptive pain coping strategies. We found a significant difference in the dimension 'distraction' for the CRPS+, but no other significant differences for the total scores and the other dimensions of the PPCI were found. We restrained from further evaluation since no relevant norm data were available for further comparison. In conclusion, pain adaptive coping mechanisms were used by all subjects, which probably reflects that a large proportion of the subjects had ongoing CRPS and/or other pain. Utilizing 'distraction' for pain coping has been associated with a higher degree of depressive symptoms and anxiety [19], which also was seen in our population with affected mental health with phobias and OCD, and the health-related quality of life and mental functioning by SDQ were affected as well. This is in concurrence with Bean et al. [28] and Tan et al. [9], who found that both previous and current CRPS have long-term psychosocial consequences for adults, but not with Wager et al. [2] and Logan et al. [10]. When reflecting on our findings concerning prognosis for current or relapse of CRPS for the former childhood CRPS subjects, the relative number of subjects still in pain and being treated for pain would indicate a worse prognosis for CRPS in accordance with Bean et al. [28]. When compared to normative data of SDQ, social functioning seems overall to be affected, and especially the ability to have 'social strength' seems affected when compared to healthy children. This concurred with the comparison to the normative data of DSM-IV, where we also found that early-life CRPS seems to affect mental health in the long term. For the quality of life, we compared normative data from young healthy adults and young adults with fibromyalgia. The subjects with former childhood CRPS had a better score than the fibromyalgia group, but a worse score than healthy young adults. Especially, 'physical function' and 'school function' were affected when evaluated by the child. This is in concurrence with Assa et al. [29], who

found that children with chronic pain have compromised school functions with decreased school attendance. Interesting, the overall evaluation by parents for the subjects was similar to that of healthy young subjects, and there were no significant differences in total scores or the four dimensions when having CRPS, CRPS– or other pain. Parents evaluated 'school function' better than the children. The subjects with CRPS+ had a poorer score for physical function. In conclusion, health-related quality of life is affected by former childhood CRPS patients in the long-term, when compared to healthy young adults, but less than for fibromyalgia.

We acknowledge that our study does have limitations. As with other similar long-term CRPS retrieval studies, our sample size is small increasing the risk of a type II error [3, 8], thus having sub-categories, as in this study, precludes achieving power in the statistical analyses. Our study is, as mentioned earlier, suggestive and hypothesis-generating and should be interpreted as such. The prevalence of CRPS is low, and acceptable sample sizes can only be properly achieved by multicenter studies. Moreover, due to the retrospective nature of the study, baseline data for patients (initial symptoms) were not recorded systematically, and we relied on chart data. Thus we are unable to determine if subjects could remember the specific nature of symptoms of their condition at the time of initial treatment. However, we examined the subjects' charts to determine if their type and anatomical location of CRPS pain, as well as the treatment, were corresponding with symptoms at the current examination. Likewise, we included parents to help them recollect their clinical history. Ideally, all examinations, questionnaires, and interviews also should have been performed before treatment for longitudinal comparison as well using validated questionnaires targeting the specific patient group and being linguistically validated. Moreover, due to the nature of our retrospective study, we were unable to provide an adequate control group that has had a previous long-term pain condition. We needed to rely on comparing reference data from healthy, typically developed children. Using an adequate group for comparison is debated, and some authors advocate and prefer using another chronic pain population instead of healthy subjects [2, 9]. In this study, this was demonstrated when comparing normative data from patients with fibromyalgia. We would suggest that future studies consider the above-mentioned factors to minimize confounders.

In conclusion, this exploratory study found that one-third (7/22) and one-half (12/22) of the former subjects with childhood CRPS 1 have ongoing CRPS and other pain affecting their daily life. Childhood CRPS 1 seems to have long-term psychosocial consequences and poorer quality of life than age-related healthy peers. Clinical follow-up longer than at least 4 years is recommended to capture relapse of CRPS 1 and as important to treat other pain affecting daily living. In future studies, research into whether or not the bio-emotional and psychosocial factors are preexisting, as well as if life-changing events, family environment, and school relationships have an etiological role or are derived from the CRPS condition, would increase the understanding of the long-term consequence of childhood CRPS 1. It is also important to include treatment of other comorbid pains, which might affect the CRPS [30].

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